CHAPTER 4
QUANTIFICATION OF HEALTH EFFECTS CHANGES

4.1 BACKGROUND ON HEALTH EFFECTS STUDIES

Several different types of health effects studies are used to measure health responses to environmental pollutants. Different types of studies provide different types of information. Each type of study has different strengths and weaknesses, including variations in the types of health effects that can be considered. Some types of evidence are better suited for use in a quantitative assessment. The brief background review of health effects studies provided in this section is intended to help place the assessment in context for those policy makers who may not be familiar with the health effects literature. Strengths and weaknesses of the assessment are integrally linked to those of the scientific literature upon which the quantitative assessment is based.

4.1.1 Types of Health Effects Studies

The types of studies that provide evidence of health effects following exposure to sulfate aerosols include epidemiology and field studies, human clinical studies, and laboratory and toxicology studies.

Epidemiology and Field Studies

Epidemiological and field studies for sulfate aerosols typically involve estimation of a statistical relationship between the frequency of specific health effects observed in a study population in its normal environment and sulfate aerosol concentrations measured at stationary outdoor monitors in the study area. These studies are therefore able to provide "concentration-response" functions that can be used to estimate the change in the frequency of health effects for a population in its normal environment that would be expected to occur with specific changes in ambient outdoor sulfate aerosol concentrations. A concentration-response function is a quantitative relationship between ambient levels (concentration) of a pollutant and the frequency of specific health effects in a given time period (response). For example, it may give the percentage of study subjects who report cough symptoms on a given day as a function of the concentration of ambient sulfate aerosol on that day.

Epidemiology and field studies often involve time-series analyses of changes in rates of health outcomes within a specific area, sometimes for a pre-selected sample, as air pollution concentrations fluctuate. An example of this study design would be daily observation and recording of asthma symptoms with a pre-selected group of subjects with diagnosed asthma, and

statistical analysis to determine if there is an association between the frequency of the symptoms and fluctuations in sulfate aerosol concentrations from day to day. Epidemiology studies may also use cross-sectional data, looking at differences in health outcomes across several locations at a selected point or period of time. This may involve, for example, a comparison of the prevalence of chronic respiratory disease in different cities with different average sulfate aerosol concentrations. Although cross-sectional studies have the advantage of being able to consider potential effects associated with long-term exposures, it can be very difficult to fully control for potential confounding factors. Time-series studies reduce many of the problems associated with confounding or omitted variables because the same population group is studied over time, but weather and seasonal variation that may be correlated with sulfate aerosol concentrations can pose some similar problems.

Time-series and cross-sectional epidemiology studies can be either cohort studies or population studies. Cohort studies analyze the incidence of health effects in a sample of identified individuals usually selected specifically for the study. For example, a cohort might be a group of study subjects who record daily symptoms for a period of time. A cohort study might also collect data on the health status of a selected sample of individuals and then do a follow-up on the same individuals after a specified length of time to determine what changes in health status have occurred for each individual. Population studies, on the other hand, rely on data available for the population as a whole rather than tracking the effects on specific individuals. For example, a population study may analyze daily mortality rates in a given location as they related to daily particulate matter concentrations. Another example of a population study is a comparison of the prevalence of chronic respiratory disease in different locations with different average pollution concentrations. In general, cohort studies are preferred because characteristics of the individuals in the study sample can be determined, allowing better control for other risk factors, such as smoking or diet. Population data are, however, readily available for many types of health effects and therefore provide an opportunity to conduct epidemiology analyses very cost effectively.

One of the strengths of epidemiology studies is that they analyze actual health effects in human populations at ambient pollution concentrations. Subjects are studied in their normal environment and the health effects are directly observed. A major challenge for epidemiology studies is the difficulty in isolating with confidence the effects of a specific air pollutant such as sulfate aerosol when this may be just one of many complex factors that influence human health. Finding a statistically significant correlation between a health effect and exposure to sulfate aerosols does not prove causality. To support an inference of causality, epidemiology results need to be supported by repeated observation in different studies and by biological plausibility and consistency with evidence from other types of health effects studies.

Human Clinical Studies

Human clinical studies, sometimes also called chamber studies, examine the response of human subjects to pollutant exposures in a controlled laboratory setting. The response of the individual

can be monitored and the environment controlled so that the effects of one pollutant can be isolated. Clinical studies on sulfate aerosols have typically exposed subjects to specific sulfate aerosol concentrations for one or several hours and measured responses such as pulmonary function or respiratory symptoms, sometimes in combination with moderate or vigorous exercise. Clinical results can provide evidence of causation because confounding factors are well controlled.

Clinical studies are limited to consideration of short-term reversible health effects that can be purposely induced in human subjects. Also, the health effects of short-term exposure to sulfate aerosols may be different in the everyday environment where other pollutants are also present and the individual's behavior and activities are quite varied. Clinical results are also limited for the purposes of extrapolation and generalization because sample sizes are usually quite small, making generalization somewhat difficult. Clinical results, in combination with supporting epidemiology results, can support an inference of causality between pollution exposure and observed health effects.

Laboratory and Toxicology Studies

Laboratory and toxicology studies use animal subjects, and sometimes human tissue or cells, to study biological responses to pollutants in a controlled laboratory setting. Animal organs and tissue can be directly examined for effects of acute and chronic exposures, revealing a wealth of information about biological responses to sulfate aerosol exposures. These studies provide a great deal of useful and important information about the specific biological pathways and mechanisms by which pollutants cause harm to living organisms. For example, laboratory studies may provide direct biological evidence of how a pollutant decreases the ability of a living organism to defend against disease and infection.

4.1.2 Advantages and Limitations for Assessment Purposes

For a quantitative assessment of the human health benefits of Title IV, we want answers to the following questions:

- How many cases of each specific type of health effect will be avoided because of Title IV?
- How much does the exposed population value the reduction in these health effects?

Epidemiology Advantages and Limitations

For addressing the first question, many epidemiology studies provide sufficient information to infer a concentration-response function, which typically gives a quantitative relationship between the incidence of a given health effect and ambient outdoor air pollutant concentrations. A concentration-response function can be used to predict a change in the number of cases of a given health effect for an estimated change in ambient outdoor pollutant concentration.

Epidemiology-based concentration-response functions available in the literature pertaining to airborne sulfates correlate observed changes in health status or symptoms with ambient outdoor sulfate concentrations. Everyday human activity patterns and specific pollutant doses associated with specific outdoor pollutant concentrations are implicit in the concentration-response functions. Changes in incidence of specific health effects can therefore be estimated as a function of changes in ambient outdoor pollutant concentrations without conducting detailed pollution exposure modeling, as long as we accept the assumption that the human activity patterns will not change significantly when ambient outdoor pollutant concentrations change. There are implicit assumptions in this approach that the relationship between outdoor concentrations and individual exposure that exist in the original study populations are the same in the assessment population.

Epidemiology studies are also useful in addressing the second question because they are able to define health effects in terms of factors that can be directly related to perceived welfare, such as risks of premature death or days with noticeable respiratory symptoms. By drawing on available health data such as vital statistics and national health surveys, or observing changes in health over time for a panel of study subjects, epidemiology studies are able to consider a wide range of health effects. This includes very serious health effects such as premature mortality or chronic disease that are not possible to study with human subjects in controlled exposure environments. Epidemiology studies can be designed to consider potential effects of long-term exposures to air pollutants as well as short-term effects. This is an additional advantage over clinical studies.

The primary limitation in using epidemiology results for predicting changes in health effects as a function of changes in ambient air pollutant concentrations is the uncertainty about whether the causal factors for the observed association with health effects have been fully and accurately specified. Inaccurate predictions could occur, for example, if the actual causal factor is some unspecified pollutant that is highly correlated with the specified pollutant. Thus, a change in the specified pollutant would not necessarily result in a change in health effects, unless the unspecified pollutant were to also change in the same proportion. This source of uncertainty is always present in epidemiology results to some extent, and the potential for error is difficult to quantify because the extent of unspecified, and correlated, causal factors is unknown.

There may also be other important inaccuracies in the specification of the relationship between health effects and ambient air pollutant concentrations in an epidemiological study. Functional forms for the concentration-response relationship and averaging times for pollutant concentrations

are examples of things that might be misspecified, resulting in inaccuracies in predictions of health effects changes. For example, if a linear relationship is specified but the actual relationship is significantly nonlinear, the predicted estimates could be either too high or too low, depending on the shape of the actual relationship. These sources of uncertainty are also difficult to quantify because the extent of the error in the original epidemiological specifications is unknown. Uncertainties are greater if epidemiology results are extrapolated beyond the range of concentrations over which the original results were estimated.

Clinical Advantages and Limitations

Clinical study results provide information about the relationship between exposure and health response obtained in a controlled environment. Thus, concerns about whether the observed relationship is actually causal are reduced. Relationships between exposure and response are more accurately measured in the controlled environment of the clinical study. This is in contrast to most epidemiology studies which use ambient outdoor pollutant concentrations as the measure of exposure. Clinical studies therefore provide potentially more accurate, or at least more convincing, dose-response information than is obtained with epidemiology studies. This is an important advantage of clinical study results for quantitative assessment purposes.

There are two significant limitations of clinical study results when it comes to a quantitative assessment of changes in health effects as a function of changes in outdoor pollutant concentrations. First, clinical study results for quantitative assessment purposes are limited because only a small range of exposures and potential health effects can be considered in clinical studies. Clinical studies are generally confined to short-term exposures and to health effects that are reversible and not life-threatening. It is simply not possible to confine human subjects to controlled environments for extended periods of time or to attempt to induce permanent or life-threatening health effects. Clinical results are therefore unable to provide information on the full range of potential health effects of pollutant exposures, if long-term exposures or permanent or life-threatening health effects are suspected.

Second, using clinical study results requires some type of quantitative exposure analysis to link changes in outdoor ambient air quality to pollutant exposures as measured in the clinical (indoor) study setting. This typically requires some analysis or assumptions about how much time people spend in various environments (e.g., indoor, outdoor, automobile) and about the relationship between outdoor pollutant concentrations and pollutant concentrations in each of the other types of human environments. Thus, several extra steps are added to the analysis relative to what is needed when epidemiology study results based on outdoor pollutant concentrations are used.

Two quantitative assessments conducted recently for changes in ambient ozone concentrations provide examples of assessments that have used some available clinical-based dose-response information for acute respiratory symptoms as a function of controlled ozone exposures (Krupnick and Kopp, 1988; Hall et al., 1989). These studies illustrate the difficulty in applying

clinical dose-response functions because of the need for detailed exposure analysis; they also provide an interesting comparison between results obtained using epidemiology-based concentration-response functions and clinical-based dose-response functions for the same type of health effect: acute respiratory symptoms.

The clinical studies used in these two assessments provided data on whether respiratory symptoms occurred with subjects exposed to controlled concentrations of ozone while exercising for one, two, or seven hours. To utilize these results to estimate how a change in ozone concentrations in the ambient outdoor air would affect the frequency of respiratory symptoms for a population in its everyday environment, either extensive modeling or assumptions must be used regarding population activity patterns and resultant ozone exposures. Hall et al. (1989) developed a detailed ozone exposure model for the South Coast Air Basin. They found that estimates of the frequency of respiratory symptoms based on the clinical results and the exposure modeling were higher per unit of ambient outdoor ozone relative to the results obtained using available epidemiology study results. Krupnick and Kopp (1988) did not conduct detailed exposure modeling, but rather used a range of alternative assumptions regarding activity patterns and exposures. They obtained estimates that were either higher or lower than the epidemiology-based estimates, depending on the assumptions used in the exposure portion of the analysis.

Laboratory Advantages and Disadvantages

Laboratory study results have the same advantage as that discussed above for clinical study results: pollutant exposures are well controlled in a laboratory setting and variations in confounding factors are reduced. The analyst therefore has more confidence that the observed relationships are causal and that the measured dose-response functions are accurate. Laboratory studies also have the potential to consider the effects of long-term as well as short-term exposures, which extends the range of health effects that might be considered relative to clinical studies.

Laboratory study results have three important limitations when it comes to a quantitative assessment of changes in health effects as a function of changes in pollutant emissions. Similar to clinical study results, using laboratory study results requires some type of quantitative exposure analysis to link changes in outdoor ambient air quality to pollutant exposures as measured in the laboratory study setting. Thus, an extra step is added to the analysis relative to what is needed when epidemiology study results are used. Second, laboratory studies often use animal subjects, which introduces considerable uncertainty when attempting to extrapolate quantitative results to human populations, as is needed in a quantitative assessment. Third, laboratory studies sometimes focus on health effects that are difficult to interpret in terms of specific illnesses or symptoms. Linkages between cellular and biochemical concentration changes and clinical manifestation of illness are often difficult to quantify.

4.2 SUMMARY OF HEALTH EFFECTS EVIDENCE FOR SULFATE AEROSOLS

This section provides a brief summary of the available health effects evidence concerning sulfate aerosols and other fine particulates ($PM_{2.5}$). This summary is not intended to be a comprehensive review. Its purpose is to highlight the range of available evidence, list the kinds of health effects that have been observed, and to focus specifically on health effects that have been found in association with sulfate aerosols because they are the focus of this assessment. Many of the health effects listed here have also been found to be associated with $PM_{2.5}$ concentrations in locations where sulfate concentrations are low, so none of the findings reported here and elsewhere in this report should be interpreted as suggesting that sulfates are the only harmful constituent of $PM_{2.5}$.

Detailed reviews of available health effects evidence for inhalable particulate matter, including sulfate aerosols, covering results from laboratory, clinical, and epidemiology studies, are provided in the EPA criteria documents and other documents (U.S. EPA, 1982, 1986a, 1986b, 1989, 1995). Additional reviews of part or all of this literature include Ferris (1973), Graham et al. (1990), American Thoracic Society (1991), Gong (1992), Folinsbee (1992), and Lipfert (1994).

4.2.1 Epidemiology Study Findings

A detailed discussion of epidemiology study findings is presented in Section 4.4, including identification of specific concentration-response functions selected for use in this assessment. This section gives an overview of the types of health effects that have been observed in epidemiology studies concerning sulfate aerosols and $PM_{2.5}$.

Epidemiology studies conducted to date provide evidence of statistically significant associations between ambient outdoor concentrations of sulfate aerosols or $PM_{2.5}$, or both, and the following human health effects:

- **Premature mortality.** Evidence has been found in prospective cohort and cross-sectional studies of an association between mortality rates in different locations and average sulfate concentrations in those locations (e.g., Pope et al., 1995). Evidence has also been found in time-series studies of an association between daily mortality rates and sulfate concentrations in several urban areas in the United States and elsewhere (e.g., Dockery et al., 1992).

- **Chronic respiratory disease.** Prospective studies have found higher rates of chronic respiratory disease in locations with higher $PM_{2.5}$ concentrations (e.g., Abbey et al., 1995).

- **Hospital admissions.** Time-series studies show a correlation between daily hospital admission rates and daily sulfate concentrations (e.g., Burnett et al., 1995).

- **Aggravation of asthma symptoms.** Time-series studies with panels of diagnosed asthmatics who record their symptoms and medication usage each day have found an association between the aggravation of asthma symptoms and daily sulfate concentrations (e.g., Ostro et al., 1991).

- **Restricted activity days.** Self-reported number of days on which activities are restricted because of illness during a 14-day recall are recorded in a national sample through the Health Interview Survey. The frequency of such days has been found to be significantly associated with the average $PM_{2.5}$ concentrations in the city of residence during the same 14-day period (e.g., Ostro and Rothschild, 1989).

- **Acute respiratory symptoms.** In a study during which a panel of healthy subjects recorded daily respiratory symptoms, the frequency of such symptoms was found to be correlated with daily sulfate concentrations in the study location (e.g., Ostro et al., 1993).

Taken as a whole, the available epidemiology evidence shows a strong relationship between sulfate aerosols, and other fine particulates, and respiratory-related illness in the United States. The types of illness range from severe acute and chronic illnesses that are associated with increases in risks of death to mild acute symptoms such as coughing and wheezing. There is epidemiology evidence of health effects for both short-term fluctuations in sulfate concentrations within a given location and long-term variations in sulfate concentrations across locations.

4.2.2 Clinical Study Findings

Several studies have examined the health effects of humans exposed briefly through inhalation to moderate concentrations of sulfate aerosols in the form of sulfuric acid (e.g., Amdur et al., 1991; Koenig et al., 1993). The effects observed in some of these acute exposure studies include decreased pulmonary function and decreased bronchial clearance rates.[1] Graham et al. (1990) review this literature and conclude that acute exposures to some acidic sulfates can increase airway resistance, decrease pulmonary function, and increase responsiveness to bronchoconstrictors, especially in asthmatics, but that considerable variability in the results of different studies suggests uncertainty about which exposures will reproducibly cause these effects.

Decreased pulmonary function in the form of increased airway resistance has been noted in some studies for both adult and adolescent asthmatics following inhalation exposure to sulfuric acid during exercise (Amdur et al., 1991; Koenig et al., 1993). In adult asthmatics, inhalation exposure to 450 $\mu g/m^3$ sulfuric acid for 16 minutes resulted in an increase in airway resistance, whereas exposure to 100 $\mu g/m^3$ caused no response (Amdur et al., 1991). In adolescent asthmatics, inhalation exposure to 68 $\mu g/m^3$ sulfuric acid for 40 minutes resulted in increased airway

[1] This section provides just a brief overview of clinical study findings and draws upon the summary of clinical research on this topic provided by Admur et al. (1991).

resistance. The increase in airway resistance of adolescent asthmatics was greater following exposure to a combination of sulfuric acid and 0.1 ppm sulfur dioxide (Amdur et al., 1991). No increase in airway resistance was observed following acute inhalation exposure of nonasthmatics to 1,000 $\mu g/m^3$ sulfuric acid.

Bronchial clearance, a major defense mechanism employed by the body following inhalation of irritant particles, decreased following inhalation exposure to moderate concentrations of sulfuric acid. Studies in humans show that inhalation exposure to less than 200 $\mu g/m^3$ sulfuric acid for one hour stimulates clearance in larger airways; however, clearance is depressed in small airways where more acid deposits. Clearance is restricted in both small and large airways following exposure to 1,000 $\mu g/m^3$ sulfuric acid (Amdur et al., 1991). At exposure concentrations of 100 $\mu g/m,^3$ increasing the exposure time from one to two hours results in an even greater decrease in bronchial clearance, and a persistent reduction in clearance of particles for up to three hours following exposure (Amdur et al., 1991).

The effects noted (i.e., decreased bronchial clearance and decreased respiratory ability) are similar to some of the effects observed in epidemiological studies, including increased incidence of acute respiratory symptoms and depressed lung function (American Lung Association, 1978). However, as described in Section 4.1, these studies are limited for the following reasons:

- Exposure was limited to either sulfuric acid or a combination of sulfuric acid and sulfur dioxide. Synergistic or antagonistic interactions between air pollutants would not be represented in these studies.

- Because of the inherent and understandable limitations of clinical studies, health effects resulting from chronic exposure to sulfate aerosols cannot be observed in clinical studies. It is possible that effects over a longer duration would be more pronounced. Continuous exposure to ambient aerosols results in the simultaneous deposition and redistribution of particles, causing changes such as marked and persistent depression in bronchial clearance, whereas acute exposure results in an initial rapid clearance of inhaled particles (U.S. EPA, 1986a). Indeed, animal exposures show a pattern of decreased clearance that continues well after exposure has ceased.

- The sample size of the exposed populations was quite small, making extrapolation to the actual exposed populations difficult. Additionally, sample demographics were not representative of actual exposed populations.

- The body of work on the effects of sulfuric acid on pulmonary function is not fully consistent, and concentration-response relationships have not yet been demonstrated (Graham et al., 1990).

4.2.3 Animal Toxicological Study Findings

Acute Exposure Animal Studies

The effects of acute inhalation exposure to sulfate aerosols (in the form of sulfuric acid) in animals have been described in several studies. The studies used a variety of species, including mice, rats, guinea pigs, dogs, donkeys, rabbits, and monkeys. Although some studies failed to cause effects in exposed animals, a number of studies show respiratory effects increasing with concentration and decreased particle size. Observed effects, including respiratory system damage, increased airflow resistance, and decreased function of the body's defense mechanisms, are summarized below.

Respiratory system injury, including lesions in the bronchi, bronchioles, larynx, and trachea, was noted in mice and guinea pigs following short-term exposure to high concentrations (60 to 125 mg/m^3) of sulfuric acids (Lee and Mudd, 1979). These are, however, much higher concentrations than are typical of ambient conditions in the United States.

Increased airflow resistance occurred in exposed animals, the magnitude of which is related to both concentration and particle size. At concentrations below 1 mg/m^3, a greater response was observed for 0.3 µm than for 1 µm particles (Amdur et al., 1991; Chen et al., 1991). Significant airflow resistance continued up to at least one hour following exposure, and persisted longer than flow resistance resulting from exposure to sulfur dioxide (Amdur et al., 1991; Chen et al., 1991).

A decreased ability in mechanisms enabling the body to respond to disease and infection was noted (Lee and Mudd, 1979; Amdur et al., 1991). One study determined that a single inhalation exposure to concentrations of sulfuric acid at concentrations that occur in the ambient air decreased the body's resistance to infectious disease (Zelikoff and Schlesinger, 1992). The body's defense mechanisms are impaired as described below:

- There is a decrease in production of interferon, which provides resistance to viral infections (Lee and Mudd, 1979).

- A decrease in bronchial clearance occurs (Amdur et al., 1991; Fujimaki et al., 1992). As described above, bronchial clearance is one of the body's defense mechanisms.

- The release of histamine, a compound believed to cause allergic reactions, is increased. This suggests that sulfuric acid might be one cause of allergic diseases (Fujimaki et al., 1992).

- Both phagocytic activity of macrophages and superoxide production are decreased following inhalation exposure to relatively low concentrations of sulfuric acid (Schlesinger et al., 1992). This decreased function compromises the cellular ability to defend against infection and disease.

Although these findings are consistent to a certain degree the effects observed in epidemiological studies, such as increased respiratory infection and decreased respiratory function in children, it is difficult to determine their applicability for the following reasons:

- Exposures were brief, rather than the daily long-term exposure typical of air pollution exposure.
- Interaction among various air pollutants was not studied.
- Extrapolation of animal findings to humans contains a degree of uncertainty.

Chronic Exposure Animal Studies

There are few laboratory studies describing the effects of chronic inhalation exposure to sulfuric acid, however, observed effects included pulmonary damage, decreased airflow, and decreased bronchial clearance. In one study, monkeys were exposed for two years to 160 $\mu g/m^3$ of sulfur as 0.54 µM of sulfuric acid. This exposure resulted in moderate to severe pulmonary damage, and decreased airflow (Amdur et al., 1991). Bronchial clearance was decreased in both rabbits and donkeys following chronic exposure to concentrations of sulfuric acid ranging from 100 to 250 $\mu g/m^3$; a continued decrease was noted in both species for up to three months after the final exposure (Schlesinger et al., 1979; Gearhart and Schlesinger, 1988, 1989). Although there is uncertainty regarding the extrapolation of exposure concentrations from animals to humans, these studies suggest the possibility of respiratory injury due to chronic exposures to sulfuric acid. It is uncertain whether these exposures are relevant to human populations in the United States at current ambient sulfate concentrations.

4.3 ISSUES IN APPLYING EPIDEMIOLOGY RESULTS IN THIS ASSESSMENT

This quantitative assessment relies on concentration-response functions from the available epidemiology literature concerning human health effects associated with sulfate aerosols, and in some cases $PM_{2.5}$. Available epidemiology results were selected for quantitative use in this assessment for the following reasons:

- Epidemiology results are based on studies of actual human health data and associated pollution exposures. Extrapolations from animal responses or from artificial clinical exposures are not necessary.
- A large available body of relevant epidemiology literature allows a quantitative assessment to be performed using a modest amount of research resources.

- Available epidemiology results cover a wide range of suspected health effects, including responses to long-term as well as short-term exposures.

- Reasonable assumptions can be employed when applying epidemiology results to calculate changes in health effects as a function of estimated changes in outdoor sulfate concentrations that allow the assessment to be conducted without doing detailed human exposure modeling.

- Epidemiology results are available for health effects that readily lend themselves to monetary valuation, such as premature mortality risks and self-reported symptoms.

The basic approach used in this assessment of applying epidemiology results to estimate health effects changes associated with estimated changes in outdoor air pollutant concentrations has been used in previous assessments for various air pollutants. These include EPA's Regulatory Impact Analyses for particulate matter and sulfur oxides (U.S. EPA, 1984, 1986c, 1988). Other assessments of the benefits of alternative pollution control strategies that used epidemiology results to estimate health benefits include Rowe et al. (in press), Krupnick and Kopp (1988), Hall et al. (1989), Harrison and Nichols (1990), and Thayer (1991).

Applying available epidemiology results to construct specific concentration-response functions for changes in ambient sulfate aerosol concentrations requires specific interpretations and assumptions. This section presents some of the key issues that must be considered, and explains the approaches chosen for this assessment. Whatever choices that are made on each of these specific issues, considerable uncertainty remains in the final results. Using these types of epidemiology results for quantitative assessments of health risks is not universally supported by all health researchers. Concerns exist about the accuracy of the estimated quantitative relationships in epidemiology studies, the fact that epidemiology studies can show an association but do not prove causation, and about transferring results from a specific study context to an assessment context that invariably has some different characteristics.

4.3.1 The Effects of Sulfates versus Other Particulates

Title IV requirements will result in a large reduction in SO_2 emissions, primarily from sources located in the eastern United States. Sources in the western United States are subject to the same emissions limits, but few sources in the western United States currently exceed the Title IV emissions limits. The reduction in SO_2 emissions in the eastern half of the United States will result in a significant reduction in ambient airborne concentrations of sulfate aerosols over a large geographic area. For this quantitative assessment, we want to know specifically how sulfate aerosols affect human health. However, a significant difficulty for this assessment is that epidemiology studies are limited in their ability to isolate the effects of sulfates from the effects of $PM_{2.5}$ as a whole. Because sulfates are a significant component of $PM_{2.5}$, the two pollutant

measures are typically highly correlated (Ozkaynak and Thurston, 1987). Furthermore, only a few epidemiology studies have used data on sulfate concentrations as well as $PM_{2.5}$ concentrations so only a few direct comparisons of results are available. Most use one or the other measure.

Sulfate aerosols are a significant share of $PM_{2.5}$ in the United States. In the eastern United States, the ratio of average measured sulfate concentrations to average measured $PM_{2.5}$ concentrations is about 0.4 (Dockery et al., 1993). An important underlying issue in interpreting available epidemiology results for this assessment is whether sulfates are different from other fine particulates in terms of the amount or type of adverse health effects they cause. Although it is reasonable to expect that there may be differences, available information is not sufficient at this time to specify the differences for sulfates or any other common constituent of $PM_{2.5}$. Sulfate measures have been used in many epidemiology studies, but only a few studies have made a direct comparison of results obtained when a sulfate measure is used versus a $PM_{2.5}$ measure for the same location and study population. Several such studies have found statistically significant associations with the health endpoint for both pollutant measures (e.g., Pope et al., 1995; Dockery et al., 1993). Some of these studies have found a statistically stronger association between health effects and sulfates (e.g., Plagiannakos and Parker, 1988; Ostro, 1990) and others have found a statistically stronger association with more comprehensive measures of particulates such as $PM_{2.5}$ or PM_{10} (e.g., Dockery et al., 1992; Abbey et al., 1993a).

Two of these studies (Dockery et al., 1993; Ostro, 1990) have reported sulfate and $PM_{2.5}$ coefficients for the same population groups as well as mean concentrations of each pollutant measure in the study area. We can expect that if the sulfate coefficient fully reflects the effects of all $PM_{2.5}$, or is the sole causal constituent of $PM_{2.5}$, the ratio of the sulfate coefficient to the $PM_{2.5}$ coefficient should equal the inverse ratio of the sulfate and $PM_{2.5}$ concentrations. This is true for the Dockery et al. (1993) results for premature mortality, but not true for the Ostro (1990) results for respiratory restricted activity days. The latter suggest that there is an effect of $PM_{2.5}$ that is not fully reflected in the sulfate coefficient, but that the additional effect per unit $PM_{2.5}$ is about half that for sulfate. These results are suggestive at best, because of the high collinearity between the sulfate and $PM_{2.5}$ measures, and are not sufficient for determining differences in potency between sulfate particulates and other constituents of $PM_{2.5}$.

The epidemiology evidence is abundant, however, that some or all of the constituents of $PM_{2.5}$, including sulfates, are harmful to human health. Clinical and laboratory studies provide evidence that at least some types of sulfate aerosols are harmful to the respiratory system when subjects are exposed to controlled amounts of sulfates alone. Thus, there is reason to believe that sulfates are contributing, at least in part, to the health effects observed in association with $PM_{2.5}$ and other particulate matter measures. The approach we take in this analysis to address this issue is three tiered:

- First, for health effects that have been statistically associated with sulfate concentrations, we select low, central, and high magnitudes of the estimated relationships between health effect incidence and sulfate concentrations.

- Second, for additional health effects that have been statistically associated with $PM_{2.5}$, we select low, central, and high magnitudes of the estimated relationships and apply them to the predicted changes in sulfate concentrations on the assumption that the estimated association between health effect incidence and $PM_{2.5}$ applies equally on a per $\mu g/m^3$ basis to sulfates, which are a substantial constituent of $PM_{2.5}$.

- Third, we use sensitivity analysis to determine how the results of the analysis would change if we were to assume that the estimated sulfate coefficients that form the basis of the health effects estimates in step one reflect the effects of $PM_{2.5}$ as a whole, not just sulfates, because of the typical collinearity between sulfates and $PM_{2.5}$.

For the sensitivity test on this question, we multiply all the sulfate coefficients by 0.4. This reflects an alternative assumption that the sulfate coefficient reflects the effects of other constituents of $PM_{2.5}$ as well as sulfates. This assumption and the first assumption (that the sulfate coefficients reflect the effects of sulfates only) most likely bound the "true" sulfate effect. The 0.4 adjustment is derived as follows. If we presume that sulfates and $PM_{2.5}$ are 100 percent correlated, then a coefficient estimated for a sulfate measure will reflect all the effects of the nonsulfate portion as well as the sulfate portion of $PM_{2.5}$. We might, for example, have the following estimated concentration-response relationship between a health effect (H) and sulfate levels (S), where B_s is the estimated sulfate coefficient:

$$H = B_s \times S. \qquad (4\text{-}1)$$

If, for example, B_s equals 4, this means that for every unit change in S there are 4 health effects observed. However, because of the collinearity between S and $PM_{2.5}$, B_s may actually reflect the effects of the 1 unit of S and the 1.5 units of collinear nonsulfate $PM_{2.5}$ (the ratio of measured sulfate to $PM_{2.5}$ being 0.4). Thus, if we change S by 1 unit and do not change the nonsulfate particulates, we would obtain only a 1.6 unit change in H. Therefore, B_s must be multiplied by 0.4, to calculate the health effects associated with a 1 unit change in S alone.

4.3.2 Health Effects Thresholds

Another important uncertainty in this assessment is whether there is a threshold sulfate concentration below which health effects no longer occur, or whether the slope of the concentration-response function diminishes significantly at lower concentrations. Available epidemiological evidence is inconclusive on the question. No clear threshold has been determined, but such a determination is very difficult with typical epidemiological data. Most of the

epidemiology studies reported here have estimated linear or log-linear functions that suggest a continuum of effects down to the lowest sulfate concentrations observed in the study sample, and have not attempted to identify a threshold concentration.

For this report, the default assumption adopted is that there is no threshold for health effects associated with ambient sulfate aerosols. In a practical sense, this does not mean that health effects are presumed to occur all the way down to zero sulfate concentrations because the changes in consideration (i.e., those due to Title IV) do not mean the elimination of all anthropogenic sulfate aerosols. If a threshold exists, however, it could have a significant effect on the accuracy of the results of this analysis. Depending on the level of the threshold relative to the estimated exposure concentrations, the existence of a threshold could reduce (but not increase) estimated health effects and benefits.

Because the evidence on whether, and at what concentration, there is a health effects threshold for sulfates remains inconclusive at this time, we report the results of some sensitivity analyses conducted using different assumptions regarding possible threshold concentrations for sulfate aerosols. We select two alternative threshold assumptions based on the low ends of the range of sulfate concentrations over which health effects have been estimated. The highest selected threshold for the sensitivity analysis is 5 $\mu g/m^3$. This is the mean sulfate concentration reported by Abbey et al. (1993a) for the Southern California study area for which a statistically significant association between the sulfate measure and chronic bronchitis incidence was not found. Another selected threshold is an annual average sulfate concentration of 3.6 $\mu g/m^3$, which is the lowest average sulfate concentration in the 151 cities included in the Pope et al. (1995) prospective cohort study on mortality rates in the United States. The third selected threshold for the sensitivity tests is 1.6 $\mu g/m^3$, which is the average sulfate concentration for 50 percent of the observations in the Southern Ontario study on hospital admissions (Burnett et al., 1995). This study reports a statistically significant difference for hospitalization rates between days with average sulfate concentrations of 1.6 $\mu g/m^3$ versus days with average concentrations of 4.13 $\mu g/m^3$ (the next 25 percent of the observations). This is not a direct test for a threshold, but it suggests that effects may occur at sulfate concentrations as low as 1.6 $\mu g/m^3$.

4.3.3 Uncertainty in the Estimates

The available epidemiology evidence regarding health effects associated with air pollutants, including sulfate aerosols, is subject to considerable uncertainty. Within a given study there is statistically measurable uncertainty in the estimated concentration-response coefficients, and there are differences in results obtained from different studies looking at the same or similar health effects. For each concentration-response relationship presented in this report, we have selected low, central, and high estimates. The central estimate is typically selected from the middle of the range reported in the study, or group of studies, that has been selected as providing the most reliable results for that health effect based on the study selection criteria discussed in Section 4.4.

These ranges of concentration-response values are not intended to reflect absolute upper and lower bounds, but rather ranges of estimates that are reasonably likely to be correct, given available health effects data. For example, ranges based on a single study are selected as plus and minus one confidence interval, not the absolute highest and lowest result obtained. When several different "reliable" studies are available for a given health effect, the selected range reflects the variation in results across the studies. The reader should be aware that there is analyst judgment in selecting these ranges and that the ranges do not reflect all the uncertainty in the concentration-response estimates because some of the uncertainty is not quantifiable. This is, however, an attempt to give a more realistic presentation than is given when only point estimates are reported.

Each low, central, and high estimate is also assigned a probability weight (the weights summing to 100 percent for each quantified health effect). These probability weights are used to propagate the uncertainty through the multiplication and aggregation process to total health benefit estimates. This provides an alternative to simply summing all the low estimates or all the high estimates to obtain total low and high estimates. Such simple summing can be misleading because it is highly unlikely that all the low estimates (or all the high estimates) are correct. When the low, central, and high estimates are based on results from different studies all judged as equally reliable, an equal probability weight is given to the low, central, and high estimates. When only one study is selected, the range used is plus and minus one standard error from the mean results of the study. When a statistical standard error is used, the probability weight given to the central estimate is 50 percent, with 25 percent each to the high and low estimates. In a few cases less weight has been given to a high or low estimate based on analyst judgment that there is reason to suspect that particular estimate is less likely to be correct than the other available estimates.

4.3.4 Interpretation and Aggregation of Daily Results

Many of the epidemiology studies that provide information about the health effects associated with particulate matter exposures have examined the daily incidence of a health effect such as mortality or hospital admissions, and daily sulfate concentrations. The air quality modeling used in this analysis predicts changes in annual average sulfate concentrations, not changes in the daily concentration. Therefore, it is necessary to determine how changes in annual average sulfate concentrations contribute to daily health effects.

Two types of functional forms have been used in the daily epidemiology studies. One is a linear function, in which the estimated coefficient gives the number of additional cases each day as a function of changes in the daily pollution concentration. A linear function gives the following relationship:

$$) C_i = R \times) S_i \times POP, \qquad (4\text{-}2)$$

where:

ΔC_i	=	additional cases on day i associated with a change in sulfate concentration
R	=	concentration-response coefficient between daily C and S
ΔS_i	=	change in sulfate concentration on day i
POP	=	affected population.

To obtain the number of cases each year, we sum Equation 4-2 over 365 days:

$$\sum_{i=1}^{365} \Delta C_i = R \times POP \sum_{i=1}^{365} (\Delta S_i). \tag{4-3}$$

If we multiply the right-hand side of Equation 4-3 by 365/365, we obtain:

$$\sum_{i=1}^{365} \Delta C_i = R \times POP \times 365 \sum_{i=1}^{365} \frac{(\Delta S_i)}{365}. \tag{4-4}$$

Thus, Equation 4-3 is equivalent to

Annual ΔC = R × POP × 365 × Annual average of daily changes in S.

The annual average of the daily changes in sulfate concentration is the same as the change in the annual average sulfate concentration. A linear coefficient for the daily number of cases due to sulfates, therefore, can be multiplied by 365 to obtain a coefficient for predicting the number of annual cases as function of the change in the annual average sulfate concentration.

The other common functional form is one in which the estimated coefficient gives the percentage change in the number of cases each day as a function of the daily pollution concentration. This gives the following relationship:

$$\Delta C_i / C' = R \times \Delta S_i \times POP, \tag{4-5}$$

where:

C'	=	the average daily number of cases of C due to all causes.

Equation (4-5) is simplified by substituting the average daily number of cases per individual. Once C' is moved to the right-hand side of Equation 4-5, ΔC_i can be estimated.

4.4 SELECTION OF CONCENTRATION-RESPONSE FUNCTIONS

This section provides a discussion of the specific epidemiological studies selected (based on the selection criteria discussed below) for quantitative use in this analysis. Concentration-response coefficients are selected from these studies. Ranges of concentration-response coefficients are given for each health effect category. The ranges are based on results from different studies when more than one equally applicable study is identified. All of the selected concentration-response functions are reported as functions of sulfate, based on studies that report health effects associated with sulfates or with $PM_{2.5}$.

4.4.1 Study Selection Criteria

Concentration-response functions were identified and adapted from the available epidemiology literature. These functions allow the estimation of the change in the number of cases of each health effect that would be expected as a result of changes in ambient sulfate concentrations. To be included as a basis for the concentration-response functions used in this assessment, an epidemiology study had to meet several specific criteria.

First, a proper study design and methodology were required. Studies were expected to have data based on continuous monitoring of the relevant pollutants, careful characterization and selection of exposure measures, and minimal bias in study sample selection and reporting. In addition, the studies had to provide concentration-response relationships over a continuum of relevant exposures. Second, studies that recognized and attempted to minimize confounding and omitted variables were included. For example, studies that compared two cities or regions and characterized them as “high” and “low” pollution areas were not used for quantitative purposes because of potential confounding by other factors in the respective areas and vague definition of exposure. Third, controls for the effects of seasonality and weather had to be included. This could be accomplished by stratifying and analyzing the data by season, by examining the independent effects of temperature and humidity, or by other statistical corrections.

A fourth criterion for inclusion was that the study had to include a reasonably complete analysis of the data. Such analysis would include a careful exploration of the primary hypothesis and preferably an examination of the robustness and sensitivity of the results to alternative functional forms, specifications, and influential data points. When studies reported the results of these alternative analyses, the quantitative estimates that we judged as most representative of the overall findings are those that we selected for use in this assessment. Finally, studies that addressed clinical outcomes or changes in behavior that would lend themselves to economic valuation were included. Estimates for endpoints such as changes in lung function, therefore, were not included.

4.4.2 Mortality

Over the last few decades, many epidemiologic studies have found statistically significant associations between sulfate concentrations (and other measures of particulate matter) and premature mortality among the general population. The earliest studies focused on relatively rare episodes of extremely high pollution concentrations in the 1940s and 1950s in the United States and in the United Kingdom (U.S. EPA, 1982). More recent studies have found an association at concentration levels typical of most metropolitan areas in North America.

The earliest studies of this type were cross-sectional studies examining annual mortality rates across U.S. cities with different average sulfate concentrations, often including 100 or more cities (e.g., Evans et al., 1984; Ozkaynak and Thurston, 1987). Very recently, two prospective cohort studies using individual-specific data and tracking mortality for a study sample in multiple cities over multiple years, also found an association between premature mortality and sulfate concentrations (Dockery et al., 1993; Pope et al., 1995). Time-series studies have also found statistically significant associations between daily mortality and daily fluctuations in sulfate concentrations (e.g., Dockery et al., 1992).

Some skepticism remains about whether these studies reflect a true causal relationship primarily because a biological mechanism to fully explain and verify this relationship has not been demonstrated in clinical or laboratory research (Utell and Samet, 1993). However, the epidemiologic studies are consistently finding a statistically significant association between sulfates and mortality, using different study designs and locations, and over a wide range of sulfate concentrations, including levels currently typical of many locations in the United States. It is therefore a reasonable exercise to estimate the reductions in premature mortality that might occur if sulfate concentrations were reduced, on the basis of the available epidemiologic results.

Summary of Selected Quantitative Evidence

This section does not provide a detailed review of all available literature, but focuses on results available in the literature that are best suited for the purposes of this analysis. The study selection process relied on study selection criteria discussed in Section 4.4.1, and incorporated results from prospective cohort, single-period cross-sectional, and time-series studies. From all three perspectives the results show an association between mortality and sulfate concentrations, and results from all three types of studies are relied upon in selecting a range of risk estimates for use in this analysis.

Two types of long-term exposure studies have found statistically significant associations between mortality rates and particulate matter levels in the United States. The first type is an ecologic cross-sectional study design in which mortality rates for various locations are analyzed to determine if there is a statistical correlation with average air pollutant concentrations in each location. Such studies have consistently found measurably higher mortality rates in cities with

higher average sulfate concentrations. However, concern persists about whether these studies have adequately controlled for potential confounding factors. Ozkaynak and Thurston (1987), Evans et al. (1984), and Chappie and Lave (1982) provide examples of ecologic cross-sectional studies. These studies each conducted a thorough examination of data for 100 or more U.S. cities, including average sulfate concentrations for each city, with special emphasis on the effects of including or excluding potential confounding factors such as occupations or migration. Plagiannakos and Parker (1988) combined annual cross-sectional data for 7 years for 9 counties in Ontario, Canada and also found an association between mortality rates and sulfate concentrations.

A second type of long-term exposure study is a prospective cohort study in which a sample is selected and followed over time in each location. In 1993, Dockery et al. published results for a 15-year prospective study based on samples of individuals in 6 cities. In 1995, Pope et al. published results of a 7-year prospective study based on samples of individuals in 151 cities in the United States. These studies are similar in some respects to the ecologic cross-sectional studies because the variation in pollution exposure is measured across locations rather than over time. These studies rely on the same type of pollutant exposure data as that used in the ecologic studies, which is average pollutant concentrations measured at stationary outdoor monitors in a given location. However, the mortality data are for identified individuals, which enables much better characterization of the study population and other health risks than when area-wide mortality data are used. Because they used individual-specific data, the authors of the prospective studies were able to control for premature mortality risks associated with differences in body mass, occupational exposures, smoking (present and past), alcohol use, age, and gender.

Dockery et al. (1993) found a mortality-rate ratio of 1.26 over the 15-year study period from the most polluted to least polluted city. Pope et al. (1995) found a mortality-rate ratio of 1.15 over the 7-year study period from the most polluted to least polluted city. Both of these findings were statistically significant.

The two prospective cohort studies represent a very important contribution to the study of premature mortality and sulfates (and other particulate matter measures) because the prospective design using individually identified subject allows for better accounting of other risk factors for an individual that might be confounding factors when attempting to isolate the risk associated with air pollution exposure. The findings of a significant association between mortality and sulfate concentrations in this study are very supportive of the findings in previous single-year cross-sectional studies. The prospective studies provide evidence that long-term exposures to higher average sulfate (and other particulate matter) concentrations are associated with statistically significantly higher risks of premature mortality. However, due to limitations in the measure of exposure used in these studies, it is not possible to yet determine the specific length of exposure required to obtain this result, or whether there may be some latency between elevated exposure and elevated risk. This is because the studies have used measures of sulfate and other particulate matter concentrations at the beginning of or during part of the study period as the measure of exposure. Lifetime cumulative exposures are not known. Current period concentrations are

probably correlated with lifetime exposures for individuals residing in a given location, but quantitative extrapolation from the results based on this exposure measure are uncertain.

The results of the two prospective studies and four selected cross-sectional studies are summarized in Table 4-1. Results are reported in terms of the estimated percentage change in mortality in the study sample for every $\mu g/m^3$ change in average sulfate concentrations. For example, the Pope et al. results for 151 U.S. cities indicate that for every one $\mu g/m^3$ increase in average sulfate concentrations where subjects live is associated with a 0.75 percent increase in observed mortality in the 7-year study period. The cross-sectional studies typically report results from many different specifications of the mortality regressions, because the intent of some of these studies was to test for the effect of changes in the specification. The results reported here are selected from the middle to low end of ranges of results reported, and are drawn from specifications that include the significant explanatory variables identified in addition to the air pollutant measures.

The results with respect to sulfates fall between 0.3 percent and 1.4 percent, with the exception of the sulfate result for the 6-cities prospective study, which is substantially higher. The results of the prospective studies are generally equal to or higher than the results of the cross-sectional studies, which supports that the cross-sectional results are meaningful, not just spurious statistical associations, and suggests that more accurate accounting of individual mortality risks results in greater risk attributed to air pollution exposure. This conclusion is tentative until more prospective cohort studies have been completed and continue to verify this finding.

In some studies the premature mortality result is also analyzed per unit of $PM_{2.5}$, and this is also shown in Table 4-1. When estimates are reported for both pollutant measures, these are based on estimates that do not account the other pollutant measure. They should therefore be interpreted as different measures of the same health effect based on different but highly collinear measures of fine particulate concentrations. For the Pope et al. results, the ratio of the effects of sulfate to $PM_{2.5}$ exceeds the inverse of the ratio of the mean concentrations of

Table 4-1
Comparison of Selected Mortality Study Results

Study	Study Design	Time Period	Study Location	% Change in Mortality per µg/m^3	
				SO_4	$PM_{2.5}$
Pope et al. (1995)	Prospective Cohort	1982-1989	50 U.S. cities 151 U.S. cities	 0.75%	0.69%
Dockery et al. (1993)	Prospective Cohort	1974-1989	6 U.S. cities	3.25%	1.40%
Ozkaynak and Thurston (1987)	Cross-Sectional	1980	98 U.S. cities	0.77%	
Evans et al. (1984)	Cross-Sectional	1960	98 U.S. cities	0.29%	
Chappie and Lave (1982)	Cross-Sectional	1960 1969 1974	117 U.S. cities 112 U.S. cities 102 U.S. cities	0.50% 0.54% 1.37%	
Plagiannakos and Parker (1988)	Cross-Sectional	1976-1982	9 Ontario counties	0.50%	

each measure in the study areas. This suggests that the sulfate effect exceeds the $PM_{2.5}$ effect on a per µg/m^3 basis, but suggests that there are additional effects picked up by the $PM_{2.5}$ coefficient that are not fully reflected in the sulfate coefficient. The Dockery et al. results, however, suggest that there may be no additional $PM_{2.5}$ effects other than those reflected in the sulfate coefficient.

There have also been a substantial number of daily time-series studies examining the relationship between daily mortality and daily particulate matter concentrations in many cities in North America. Dockery and Pope (1994) review and summarize these studies. These studies have for the most part used TSP or PM_{10} as the measure of particulate concentration. One time-series study (Dockery et al., 1992) reports a sulfate coefficient of 0.6 percent change in daily mortality per µg/m^3 sulfate, which is within the range of results reported in Table 4-1. Dockery and Pope report that overall, the results of the time-series studies range from 0.05 percent to 0.15 percent higher mortality for every µg/m^3 increase in 24-hour PM_{10}. This range falls just below the range of results reported for sulfates in Table 4-1 from the cross-sectional and prospective studies.

Evidence on Who is at Risk

The results of a time-series study in Philadelphia (Schwartz and Dockery, 1992a) provide estimates of elevated mortality risks separately for those over and under 65 years old. These results suggest that about 90 percent of the premature deaths associated with particulate matter occur in the over-65 group. This finding is consistent with the results of an early cross-sectional mortality study (Lave and Seskin, 1977). Ostro et al. (in press) found that about 80 percent of the premature deaths associated with particulate matter were in the over-65 group in their Santiago, Chile, study. In the United States, about 70 percent of all deaths are individuals 65 years old or older, so it appears that risks associated with air pollution exposure fall in somewhat greater proportion to the elderly.

As discussed in Chapter 5, the age of the individual at risk of premature mortality may have some bearing on the monetary value of changing that risk. For the purposes of this analysis, it is presumed based on evidence in Ostro et al. (in press) and Schwartz and Dockery (1992a) that 85 percent of the individuals at risk of premature mortality associated with sulfate exposures are 65 years old or older.

The results from Pope et al. (1995) show that the greatest association is with deaths associated with cardiopulmonary illness, and that elevated mortality risks are similar for both smokers and nonsmokers in higher pollution locations. Some of the time-series studies (e.g., Schwartz and Dockery, 1992a) have also found significant cause-specific mortality associations indicating that most pollution-associated deaths are cardiopulmonary related. Some of those at risk therefore probably suffer from chronic diseases that might be expected to shorten life expectancy even in the absence of air pollution. This does not, however, rule out the possibility that some of these chronic illnesses could themselves be related to air pollution exposure.

Estimation Approach for this Analysis

For this analysis, the epidemiologic results are being used to predict how mortality rates may change given a change in ambient sulfate concentrations. For this purpose, we select a range of results from the three types of mortality studies. Premature mortality is a very serious health endpoint and there is a large body of epidemiologic literature that has studied mortality as it relates to air pollutant exposure. However, there remain many uncertainties in specific quantitative interpretations of the results of the epidemiologic studies that have studied the association between premature mortality and sulfate concentrations. We therefore select a wider range of findings than those selected for most of the other health endpoints quantified in this assessment.

We select a range of four estimates to reflect the range of results obtained in the mortality studies. For a lowest estimate, we select the 0.1 percent mortality effect found for PM_{10} in the many time-series studies. This is at the low end of the range of mortality effects estimated and because it is

based on PM_{10}, applying it to an estimated change in sulfate concentration presumes that a sulfate aerosol is no more harmful than a typical PM_{10} aerosol. We select a low-central estimate of 0.3 percent based on the low end of the cross-sectional results for sulfates. We select a high-central estimates of 0.7 percent based on the Pope et al. prospective study. This is still within the range of the cross-sectional results. As a high estimate we select 1.4 percent based on the $PM_{2.5}$ results of the 6-cities study and the highest cross-sectional result reported in Table 4-1. Although there are results from some studies that are both lower and higher than this range (e.g., some time-series studies find 0.05 percent or less and the 6-cities result for sulfates is greater than 3 percent), a very large share of the findings for sulfates fall into this range. We give equal probability weights (25%) to all four of the selected risk estimates.

The selected percentage changes in mortality must be multiplied by average annual mortality to calculate the change in annual premature deaths per change in annual average sulfate concentrations. For this we use the average U.S. nonaccidental mortality rate of about 8,000 per million population per year (U.S. Bureau of the Census, 1994). For example, the low-central estimate is 0.3 percent of 8,000 divided by 1,000,000. The selected mortality risk coefficients and calculation procedures are thus:

$$\text{Low annual } SO_4 \text{ premature mortality} = 8 \times 10^{-6} \times POP_j \times (\ ) S_j) \quad (4\text{-}6a)$$

$$\text{Low-central annual } SO_4 \text{ premature mortality} = 24 \times 10^{-6} \times POP_j \times (\ ) S_j) \quad (4\text{-}6b)$$

$$\text{High-central annual } SO_4 \text{ premature mortality} = 56 \times 10^{-6} \times POP_j \times (\ ) S_j) \quad (4\text{-}6c)$$

$$\text{High annual } SO_4 \text{ premature mortality} = 112 \times 10^{-6} \times POP_j \times (\ ) S_j) \quad (4\text{-}6d)$$

where:

POP_j = total population in area j

$) S_j$ = change in annual average sulfate concentration in area j.

4.4.3 Chronic Respiratory Disease

For more than two decades, there has been some evidence suggesting that higher ambient particulate matter exposures are associated with higher rates of chronic respiratory disease. Much of this evidence, however, has been based on cross-sectional analyses, comparing disease or symptom prevalence rates in different communities with different average pollution levels (e.g., Ferris et al., 1973, 1976; Hodgkin et al., 1984; Portney and Mullahy, 1990). These studies are able to suggest a possible association, but are difficult to use for quantitative estimates of specific concentration-response functions. This difficulty stems primarily from uncertainty about how to characterize the relevant exposure units, in particular the time aspects of exposure. Chronic symptoms presumably occur as a result of long-term exposures, but cross-sectional analyses are not very enlightening about whether, for example, it is the five-year average, the twenty-year average, or the number of times a given level is exceeded that is the relevant exposure measure.

Without this information, it is difficult to predict quantitatively how risks change when exposures change.

Recently published articles (Abbey et al., 1993a, 1993b, 1995) have reported results of a 10-year prospective cohort study conducted at Loma Linda University in California with a large sample of nonsmoking adults. This follow-up allowed for measures of exposure preceding and during the 10-year study period and for obtaining information on changes in chronic respiratory disease incidence over time. Thus, development of new cases of disease were analyzed in relation to individual-specific air pollution exposure history. This study provides for the first time a more definitive concentration-response function for chronic respiratory disease. Uncertainty about the potential effect of exposures that preceded the study period, and lag times between exposure and illness onset still exists with these findings.

The Loma Linda University Study

In the first stage of the Loma Linda University study, a large sample (approximately 7,000) of Seventh Day Adventists (selected because they do not smoke), was interviewed in 1977. Health histories, current respiratory symptoms, past smoking and passive smoking exposure, and residence location histories were obtained. Hodgkin et al. (1984) compared the chronic respiratory disease status of respondents who had lived for at least 11 years in either a high or a low pollution area in Southern California. After adjusting for sex, race, age, education, occupational exposure, and past smoking history, residents of the higher pollution area were found to have a prevalence of airway obstructive disease (AOD) (including chronic bronchitis, asthma and emphysema) that was 15 percent higher than for residents in the low pollution area. Using the same 1977 Loma Linda sample, Euler et al. (1987) report results showing a statistically significant association between past TSP exposure, based on residence zip-code history, and the prevalence of chronic respiratory disease.

Abbey et al. (1993a, 1993b, 1995) report the results of a cohort study with the Seventh Day Adventist sample in 1987, which provides better quantitative concentration-response information. Nearly 4,000 subjects were interviewed in 1987 who had been interviewed previously in 1977. All were 25 years old or more in 1977. Estimates of air pollutant exposures histories were developed based on subjects' reported residence locations from 1967 to 1987 and pollutant measures from stationary outdoor monitors closest to each residence location over the study period. Abbey et al. (1993b) report results of the cohort study based on TSP data from 1973 to 1987. Abbey et al. (1995) added data on $PM_{2.5}$, based on airport visibility data from 1967 to 1987, sulfate data from 1977 to 1987, and data on gaseous air pollutants including ozone, nitrogen dioxide, and sulfur dioxide.

Several different health outcomes were examined including new cases of emphysema, chronic bronchitis, or asthma, in 1987 for those not reporting any definite symptoms of these diseases in 1977. Disease definition was based on self-reported symptoms using the standardized respiratory

symptoms questionnaire developed by the National Heart and Lung Institute for the United States. Respondents were classified as having *definite* symptoms of emphysema, chronic bronchitis or asthma if they met specific criteria for the disease diagnosis. Having definite symptoms of any one of these three was defined as definite airway obstructive disease (AOD). Having definite chronic bronchitis was defined as having symptoms of cough and/or sputum production on most days for at least 3 months/year, for 2 years or more. Emphysema and asthma required a physician's diagnosis as well as associated symptoms.

Logistic models were estimated for mean concentrations of air pollutants and for hours above selected levels for each pollutant. The regressions included independent variables for past and passive smoking exposure, possible symptoms in 1977, childhood respiratory illness, gender, age and education. Abbey et al. (1993b) report a statistically significant association between average long-term TSP exposure levels and AOD, as well as with chronic bronchitis alone.

Abbey et al. (1995) report no statistically significant associations between the gaseous pollutants and the development of new cases of chronic respiratory disease, although aggravation of existing disease was apparent, specially for asthma in relation to ozone exposure. More important, the authors conclude that exposures to gaseous pollutants did not appear to be a significant confounding factor in the measured association between particulate matter exposure and incidence of chronic respiratory disease.

Abbey et al. (1995) report statistically significant associations between TSP exposure and new cases of AOD, as well as with new cases of chronic bronchitis and new cases of asthma (which are two types of AOD); and the magnitude of the TSP results was consistent with the previous reported results (Abbey et al., 1993b). The authors also report a statistically significant association between new cases of chronic bronchitis and the $PM_{2.5}$ measure, and between new cases of asthma and the sulfate measure. The magnitudes of the reported odds ratios for new cases of AOD were similar for selected changes in TSP, $PM_{2.5}$, and sulfates, but the result was statistically significant only for the TSP measure. The authors note that there is probably more measurement error in the $PM_{2.5}$ exposure estimates because of the approximation from airport visibility, and in the sulfate exposure estimates because they were based on data from 1977 to 1987 only.

Abbey et al. (1995) also report evidence that increased severity of AOD is statistically significantly associated with TSP, $PM_{2.5}$, and sulfate exposure for those who reported definite symptoms in 1977. Thus, it appears that particulate matter exposure both aggravates existing cases and causes new cases.

Selected Chronic Bronchitis Risk Estimates from Abbey et al. (1995)

We have selected the chronic bronchitis results from Abbey et al. (1995) for $PM_{2.5}$ for quantification of changes in risks of developing chronic bronchitis in this analysis. The estimates

used in this analysis reflect only the development of new cases, not the aggravation of existing cases. The key assumption in this application of the $PM_{2.5}$ results is that sulfates contribute to this risk at an equal level per $\mu g/m^3$ as other constituents of $PM_{2.5}$. This assumption is partially, but not fully, supported by the Abbey et al. (1995) results. Limitations in both the $PM_{2.5}$ and the sulfate data available for this analysis contribute to the ambiguity in the findings. The quantitative interpretation of this assumption is to apply the risk associated with each $\mu g/m^3$ of $PM_{2.5}$ to the estimated $\mu g/m^3$ change in sulfate concentration without any adjustment to the risk value due to the difference in the particulate measure. Implicit in this is the assumption that sulfates contribute to the $PM_{2.5}$ effect only in proportion to their share of total $PM_{2.5}$ and that other constituents of $PM_{2.5}$ are equally as harmful.

The failure to find a statistically significant relationship between sulfate concentrations and new cases of chronic bronchitis is somewhat troubling with respect to this quantification approach, but it is offset to some extent by the finding of a significant relationship between sulfates and new cases of asthma (another type of AOD) and by the fact that the magnitude of the estimated relationship between AOD as a whole and sulfates is similar to the magnitude estimated for TSP and for $PM_{2.5}$, even though the statistical significance of this relationship was low for the sulfate and $PM_{2.5}$ measures.

Using the $PM_{2.5}$ results for chronic bronchitis in this assessment gives a lower risk per $\mu g/m^3$ than would have been obtained using other feasible quantification approaches based on the Abbey et al. (1995) results. For example, if we applied the estimated relative risk estimate for new AOD cases reported by Abbey et al. (1995) for 7 $\mu g/m^3$ of sulfate and attributed this risk to sulfate alone, the risk coefficient per $\mu g/m^3$ would be about 3 times higher than the selected central estimate based on the $PM_{2.5}$ results. Alternatively, if we used the statistically significant relative risk for new cases of asthma associated with a 7 $\mu g/m^3$ increment of sulfate, the risk coefficient per $\mu g/m^3$ would be about 5 times higher than the estimate based on the $PM_{2.5}$ chronic bronchitis results. Thus, although there is uncertainty in applying the $PM_{2.5}$ results, it is unlikely that they overstate the effect of sulfates on new cases of AOD as a whole.

Abbey et al. report a relative risk of 1.81 for developing a new case of chronic bronchitis during the 10-year follow-up period for an increase in average $PM_{2.5}$ exposure of 45 $\mu g/m^3$. This means that the incidence of new cases of chronic bronchitis is 81 percent higher in locations with average $PM_{2.5}$ concentrations 45 $\mu g/m^3$ higher, or 1.8 percent higher for every 1 $\mu g/m^3$ increase in average $PM_{2.5}$ concentrations. The 10-year incidence of new cases of chronic bronchitis was about 6 percent (117 ÷ 1,868 in the subsample for which $PM_{2.5}$ exposures were estimated). Thus, an individual's probability of developing chronic bronchitis in the 10-year period is $0.018 \times 0.06 = 0.0011$ per 1 $\mu g/m^3$ increase in average $PM_{2.5}$ concentration. We divide this individual risk by 10 to obtain an annual risk of developing chronic bronchitis. The high and low estimates are based on plus and minus one standard error of the estimated risk relationship. The selected low, central, and high estimates for changes in chronic bronchitis are thus:

$$\text{Low annual cases of CB} = 0.5 \times 10^{-4} \times POP_{>25j} \times (\ ) S_j) \quad (4\text{-}7a)$$
$$\text{Central annual cases of CB} = 1.1 \times 10^{-4} \times POP_{>25j} \times (\ ) S_j) \quad (4\text{-}7b)$$
$$\text{High annual cases of CB} = 2.0 \times 10^{-4} \times POP_{>25j} \times (\ ) S_j) \quad (4\text{-}7c)$$

where:

CB	=	adult chronic bronchitis
$POP_{>25j}$	=	population over age 25 years in area j
$) S_j$	=	change in annual average sulfate concentration in area j.

We apply the risk estimates to the adult population age 25 and over because this is the minimum age in the Abbey et al. study group. Chronic bronchitis takes awhile to develop and these risk estimates may not apply to younger individuals.

4.4.4 Acute Morbidity

Epidemiology studies have found health effects associated with ambient sulfates ranging from elevated rates of hospital admissions to small differences in lung function measurements. The studies selected as the basis for quantitative estimates for this report provide evidence with clear clinical significance; i.e., the effects are noticeable to subjects. This means symptoms that are noticeable to the subject and can be expected to have some impact on the individual's well-being. For this reason, we have not included studies that look only at effects on lung function. Although this may be a medically relevant health endpoint, it cannot at this time be translated into changes in symptoms or illness that can be readily valued.

Respiratory Hospital Admissions

Recent evidence indicates an association between ambient sulfates and both respiratory hospital admissions (RHAs) and cardiac hospital admissions (CHAs). Evidence of a relationship between RHAs and CHAs and sulfates, controlling for collinear ozone concentrations, is provided by Burnett et al. (1995) for Ontario, Canada. Additional evidence of a relationship between RHAs and sulfates is provided by Thurston et al. (1994) for Toronto, and by Thurston et al. (1992) for selected cities in New York. For this analysis, specific quantitative estimates are derived from the Burnett et al. (1995) Ontario study because they are for both RHAs and CHAs. The Thurston et al. studies are examined for supporting evidence, but are not used quantitatively because their results are less amenable for providing separate associations for sulfates and ozone. Supporting evidence for an effect of particles on cardiac hospital admissions is provided by Schwartz and Morris (1995).

Burnett et al. (1995) studied the relationship between hospital admissions for respiratory and cardiac disease and both sulfate and ozone from 1983 through 1988 in Ontario, Canada. Air

pollution data were obtained from a large network of monitors existing throughout Ontario. Admissions data from 168 acute care hospitals in Ontario below the 47th parallel were used. After elective admissions were excluded, counts of daily admissions for all ages and for age-specific and disease-specific categories were created. A time-series regression model was used that removed the influences of day-of-week effects, slow moving serial correlations due to seasonal patterns, and differences between hospitals. Ultimately, the effects of air pollution on deviations in the expected number of admissions to each hospital on any given day were estimated. Regression models included temperature effects and were specified with ozone and sulfate considered alone and together as explanatory variables. The results indicated that one-day lags of both ozone and sulfates were associated with respiratory admissions, and that sulfates, but not ozone, were associated with cardiac admissions. The sulfate effects were observed in both the summer and winter quarters, both males and females, and across all age groups (Burnett et al., 1995).

Thurston et al. (1992, 1994) provide supporting evidence of an association between RHA during summer months and either sulfate or ozone concentrations, or both. They do not report results for models that include both ozone and sulfate, so their results for both pollutants are likely confounded by the presence of the other correlated pollutant. However, the results are useful for rough comparison to the Burnett et al. results. Burnett et al. (1994) found that the mean sulfate concentration was associated with a 2.2 percent increase in daily summer RHAs when only sulfate was included in the model, and that the mean ozone concentration was associated with a 6.0 percent increase in daily summer RHAs when only ozone was included in the model. The single pollutant results are similar to results obtained by Thurston et al. (1992) for New York City, which were 3.5 percent for mean sulfate and 5.3 percent for mean ozone. These estimates are also reasonably consistent with the findings obtained in the Toronto study (Thurston et al., 1994).

Bates and Sizto (1989) provide some additional evidence on the issue. They estimated a stepwise regression for respiratory hospital admissions during the summer months in Ontario. First they included temperature, which explained 0.89 percent of the variance in RHA. Then they added sulfate, which increase the explained variance to 3.3 percent. When ozone was then added, the explained variance increased to 5.6 percent. This suggests that adding ozone to the regression explains about as much of the variance as that explained by the sulfate variable.

Low, central, and high estimates of RHAs associated with sulfates are selected based on the results of Burnett et al. (1995). Results were selected from a model that included both sulfates and ozone in the regression, to reduce the chance of overstating the sulfate effect because of the collinearity between sulfates and ozone in the study area. We apply a 50 percent probability to the central estimate, and 25 percent each to the low and high estimates, which are the central minus and plus one standard error. Specifically, Burnett et al. (1995) report a 3.5 percent increase in RHAs for a 13 $\mu g/m^3$ increase in sulfate when ozone was included in the model. The average daily RHA for the study period was 16.0 per million population. Thus, 3.5 percent of the 16.0 daily RHA are attributed to 13 $\mu g/m^3$ sulfate. Therefore, the daily RHA per 1 $\mu g/m^3$ sulfate is: $0.035 \times (16.0 \times 10^{-6}) \div 13 = 4.31 \times 10^{-8}$. We multiply by 365 to obtain the estimated annual

number of RHAs for a change in annual average sulfate concentration. The central estimate of changes in RHA incidence is thus as follows, with the low and high selected as the central minus and plus one standard error:

$$\text{Low annual RHA} = 1.3 \times 10^{-5} \times)S_j \times POP_j \quad (4\text{-}8a)$$
$$\text{Central annual RHA} = 1.6 \times 10^{-5} \times)S_j \times POP_j \quad (4\text{-}8b)$$
$$\text{High annual RHA} = 1.8 \times 10^{-5} \times)S_j \times POP_j \quad (4\text{-}8c)$$

where:

POP_j = total population in area j
$)S_j$ = change in annual average sulfate concentration.

Burnett et al. (1995) also reported a statistically significant association between sulfates and cardiac hospital admissions (CHA) throughout the year, while no association was found for ozone. Burnett et al. (1995) report a 3.3 percent increase in CHAs for a 13 $\mu g/m^3$ increase in sulfate when ozone was included in the model. Thus, 3.3 percent of the average daily CHAs per million population (14.4) in the study area gives the number of additional daily CHAs per 13 $\mu g/m^3$ sulfate. Dividing by 13 gives the daily CHAs per $\mu g/m^3$ sulfate [$0.033 \times (14.4 \times 10^{-6}) \div 13 = 3.66 \times 10^{-8}$]. We multiply by 365 to obtain the estimate annual number of RHAs for a change in annual average sulfate concentration. We apply a 50 percent probability to the central estimate, and 25 percent each to the low and high. The central estimate of CHAs is thus as follows, with the low and high selected as minus and plus one standard error of the central estimate:

$$\text{Low annual CHA} = 1.0 \times 10^{-5} \times)S_j \times POP_j \quad (4\text{-}9a)$$
$$\text{Central annual CHA} = 1.3 \times 10^{-5} \times)S_j \times POP_j \quad (4\text{-}9b)$$
$$\text{High annual CHA} = 1.7 \times 10^{-5} \times)S_j \times POP_j. \quad (4\text{-}9c)$$

Aggravation of Asthma Symptoms

Several studies have related particulate matter concentrations to exacerbation of asthma symptoms in individuals with diagnosed asthma. Ostro et al. (1991) report results specifically for day-to-day fluctuations in sulfate concentrations. Ostro et al. had subjects record daily asthma symptoms during the duration of the study. An aggravation of asthma symptoms was defined for each subject based on each individual's manifestation of asthma symptoms. This typically meant a notable increase in symptoms, such as shortness of breath or wheezing, and/or in use of medication relative to what was "normal" for that individual. Daily air pollution concentrations were then examined for correlations with day-to-day fluctuations in asthma symptom frequency, controlling for other factors such as weather and previous-day symptoms.

Ostro et al. (1991) examined the association between several different air pollutants, including sulfates, $PM_{2.5}$, and acidic aerosols, and aggravation of asthma symptoms among adults during

winter months in Denver. A significant association was found between the probability of moderate or severe asthma symptoms (measured as shortness of breath) and sulfate particulate concentrations, after controlling for temperature, day of study, previous-day illness, and use of a gas stove. Ozone concentrations were very low, near background concentrations, and do not create a confounding influence. The results suggest the following relationship in the winter months between sulfates and aggravation of asthma symptoms (A).

$$\text{Change in daily probability of A} = [0.0077\ (\pm\ 0.0038)/S] \times\ )\ S \qquad (4\text{-}10)$$

Using the reported sulfate mean for the study of 2.11 $\mu g/m^3$ to linearize the function yields the following calculation procedure to estimate daily probability of asthma symptoms per asthmatic based on the Ostro et al. results.

$$\text{Change in daily probability of A} = [0.0036\ (\pm\ 0.0018)] \times\ )\ S \qquad (4\text{-}11)$$

There may be an upward bias in the Ostro et al. (1991) results because the data were collected during winter months only. Winter months in Denver are also a period of more frequent respiratory colds that also aggravate asthma symptoms and may in turn cause asthmatics to be more sensitive to air pollutants. We therefore assume for the purposes of this analysis that the measured relationship between aggravation of asthma symptoms and sulfate concentrations applies during only half of the year. To annualize the relationship we therefore multiply by 182.5 rather than by 365.

Using an estimate of 4.7 percent for the portion of the U.S. population with diagnosed asthma (National Center for Health Statistics, 1992) yields the following calculation procedure to estimate annual number of asthma attacks based on the selected Ostro et al. (1991) results.

$$\text{Low annual ASD} = 3.3 \times 10^{-1} \times (\ )\ S_j) \times POP_j \times 0.047 \qquad (4\text{-}12a)$$

$$\text{Central annual ASD} = 6.7 \times 10^{-1} \times (\ )\ S_j) \times POP_j \times 0.047 \qquad (4\text{-}12b)$$

$$\text{High annual ASD} = 9.9 \times 10^{-1} \times (\ )\ S_j) \times POP_j \times 0.047 \qquad (4\text{-}12c)$$

Restricted Activity Days

Restricted activity days (RADs) include days spent in bed, days missed from work, and days when activities are partially restricted due to illness. Ostro (1987) examined the relationship between adult all-cause RADs in a two-week period and $PM_{2.5}$ in the same two-week period for 49 metropolitan areas in the United States. The RAD data were from the Health Interview Survey (HIS) conducted annually by the National Center for Health Statistics. The $PM_{2.5}$ data were estimated from visual range data available for airports in each area. Since fine particles have a more significant impact on visual range than do large suspended particles, a direct relationship can be estimated between visual range and $PM_{2.5}$.

Separate regression estimates were obtained for 6 years, 1976 to 1981. A statistically significant relationship was found in each year and was consistent with earlier findings relating RADs to TSP by Ostro (1983). The mean of the estimated coefficient for $PM_{2.5}$ across the 6 years indicated approximately 91,000 RAD each year per 1 million population for each $\mu g/m^3$ increase in annual average $PM_{2.5}$, and ranged from a low of 53,000 for the 1981 coefficient to a high of 171,000 for the 1976 coefficient.

Additional work conducted by Ostro and Rothschild (1989) added ozone measures to the regressions and found the estimated relationship between RADs and $PM_{2.5}$ to be essentially unchanged. This suggests that the RAD/$PM_{2.5}$ relationship was not confounded by the exclusion of ozone concentrations and is independent of ozone exposures. The newer work also estimated the relationship between respiratory RAD (RRAD) and $PM_{2.5}$ for employed individuals only. It was expected that this relationship might be more stable than that between all-cause RAD and $PM_{2.5}$ for all adults for two reasons: (1) it is expected that pollution induced RADs might be predominantly related to respiratory illness, and (2) workers might define a RAD more consistently than the entire adult population. It was expected, though, that confining the data to RRADs for workers might result in a smaller total number of predicted restricted activity days for a given concentration of pollution, because all effects might not be classified as respiratory and workers may be a healthier and therefore less sensitive group, on average, than all adults. The findings are consistent with this expectation. The average of the $PM_{2.5}$ coefficients for the 6 years suggested an annual increase of approximately 47,000 RRAD per 1 million population for each $\mu g/m^3$ increase in annual average $PM_{2.5}$, and ranged from a low of 31,000 for the 1978 coefficient to a high of 55,000 for the 1980 coefficient.

Ostro (1990) reports results also using data on RRADs for working adults. In this analysis he matched data from EPA's Inhalable Particles Monitoring Network on sulfates and $PM_{2.5}$, based on particulate monitors, with the HIS data for 1979 to 1981. Data on 25 cities resulted and the analysis shows statistically significant relationships between RRAD incidence and both sulfate and $PM_{2.5}$, in separate regressions as necessitated by the collinearity between the two measures of fine particulate. The quantitative results were quite comparable to the Ostro and Rothschild (1989) results for RRADs for working adults, and were also reasonably similar for sulfates and $PM_{2.5}$. Estimated annual RRADs per million population (of working adults) was approximately 56,000 per $\mu g/m^3$ sulfate or 42,000 per $\mu g/m^3$ $PM_{2.5}$.

For this analysis, we calculate changes in RAD incidence as a function of changes in ambient sulfate concentrations based on the estimated relationship between RADs and $PM_{2.5}$. The Ostro (1990) results suggest that this is a reasonable assumption, the effect of which may be to slightly understate the sulfate effect. We choose to use the $PM_{2.5}$ results for quantitative purposes because the sulfate results are available for only a subset of RADs (i.e., RRADs for working adults).

The mean results over the 6 years from Ostro (1987) for all-cause RADs for all adults (mean coefficient = 0.0048) have been selected as the central estimate for this analysis. The mean results

from Ostro and Rothschild (1989) for respiratory RADs for workers (mean coefficient = 0.0158) were selected for the low estimate. This is a low estimate because it excludes some nonrespiratory RADs that might be related to pollution exposures and is based on a healthier than average sample (i.e., workers). The selected high estimate is the mean of the two highest coefficients in the six year analysis (mean coefficient = 0.0076) by Ostro (1987). The reported coefficients give percentage changes in RADs or RRADs for a 1 $\mu g/m^3$ change in $PM_{2.5}$. Daily average estimates from the studies based on HIS data of 0.052 RAD and 0.0083 RRAD per person are used to determine the relationship between number of RADs and $PM_{2.5}$. For example, the central daily individual risk estimate is thus:

$$0.0048 \times 0.052 = 2.5 \times 10^{-4}. \quad (4\text{-}13)$$

Multiplying by 365 to estimate annual changes in RAD incidence we obtain the following low, central and high estimates for changes in annual average sulfate concentrations. The calculations are applied to the adult population 18 years and over.

$$\text{Low annual RAD} = 4.7 \times 10^{-2} \times) S_j \times POP_{\geq 18j} \quad (4\text{-}14a)$$

$$\text{Central annual RAD} = 9.3 \times 10^{-2} \times) S_j \times POP_{\geq 18j} \quad (4\text{-}14b)$$

$$\text{High annual RAD} = 14.6 \times 10^{-2} \times) S_j \times POP_{\geq 18j} \quad (4\text{-}14c)$$

where:

$POP_{\geq 18j}$ = population in location j 18 years of age and older.

Acute Lower Respiratory Symptoms

Krupnick et al. (1990) and Ostro et al. (1993) report analyses of relationships between the daily incidence of acute upper and lower respiratory symptoms among a general population panel of adults in Southern California and daily concentrations of air pollution. These health endpoints include some days with symptoms bothersome enough to result in a restricted activity day, but also include days when noticeable symptoms are present but no change in activities occurs. The statistical analyses incorporated the presence of illness on the prior day, presence of chronic respiratory disease, daily weather conditions, indoor air pollution sources, and controlled for autocorrelation.

The air pollution measures used in the Krupnick et al. analysis were coefficient of haze (COH), a measure of the visibility impairing particulates in the air, and ozone. Krupnick et al. report a statistically significant relationship between daily COH and the daily incidence of respiratory symptoms (upper and lower combined), after controlling for a statistically significant ozone effect. Ostro et al. (1993) conducted separate analyses for upper and lower respiratory tract symptoms, and added sulfates as a measure of daily particulate matter in the study area in place of the COH measure. They continued to find a statistically significant association between daily ozone and

both kinds of symptoms. They found a statistically significant relationship between daily sulfate concentrations and lower respiratory symptoms only, after controlling for ozone. We select these results for quantitative use in this assessment of changes in sulfate concentrations.

Ostro et al. (1993) report an odds ratio for incidence of lower respiratory symptoms in adults of 1.30 for a 10 $\mu g/m^3$ increment of sulfates. The average daily incidence of lower respiratory symptoms is 1.5 percent in the study sample. Thus, the average daily individual probability of having lower respiratory symptoms is $0.03 \times 0.015 = 4.5 \times 10^{-4}$ per $\mu g/m^3$ sulfate. To annualize we multiply by 365. The low and high estimates are based on minus or plus one standard error of the regression coefficient.

$$\text{Low annual LRS} = 6.6 \times 10^{-2} \times (\ ) S_j) \times POP_{\geq 18j} \quad (4\text{-}15a)$$

$$\text{Central annual LRS} = 16.4 \times 10^{-2} \times (\ ) S_j) \times POP_{\geq 18j} \quad (4\text{-}15b)$$

$$\text{Low annual LRS} = 23.0 \times 10^{-2} \times (\ ) S_j) \times POP_{\geq 18j}. \quad (4\text{-}15c)$$

Aggregation Procedures for Acute Morbidity Health Effects

Several of the more broad categories of acute morbidity health effects, such as restricted activity days or days with lower respiratory symptoms, may include days on which effects measured in another function occur, such as days spent in the hospital. To avoid double counting, therefore, it is necessary to subtract some of these potentially overlapping categories. Some additional adjustment will be necessary when one function is for all ages and another is only for adults. In this case, we will assume the incidence of the effect is proportional to the age distribution which is that 83 percent of the U.S. population is 18 and older. The following subtractions are done before monetary valuations are applied and summed. As discussed in Chapter 5 on monetary valuation of human health effects, each RHA is assumed to average 6.8 days and each CHA averages 6.9 days. We assume that all days in the hospital and all asthma symptom days are also restricted activity days and therefore subtract these from total RADs. We also assume that all RADs are also acute respiratory symptom days and therefore subtract a fraction of RADs from LRSs. The Ostro et al. (1993) study reports that 28 percent of the acute respiratory symptoms are lower respiratory tract. We therefore assume that RADs are split between upper and lower respiratory tract in the same proportions. Net RADs and net LRSs are therefore defined as follows:

net RADs = total RADs - (0.83 × 6.8 × RHAs) - (0.83 × 6.9 × CHAs) - (0.83 × ASDs)

net LRSs = LRSs - (0.28 × total RADs).

These adjustments are approximate, but they do eliminate and even possibly over-compensate for overlap in the daily health endpoints. There may remain, however, some subtle overlap between the daily health endpoints and the chronic bronchitis and premature mortality health endpoints. For example, some of the hospital admissions may reflect health effects that are accompanied by premature death. Because as is shown in Chapter 6, the total health benefits are dominated by the

premature mortality and chronic bronchitis effects, the possible impact on the total health benefits of such overlaps is necessarily small.

4.4.5 Summary of Selected Concentration-Response Functions

Table 4-2 lists the selected concentration-response estimates for each of the health effects categories for sulfates. Omissions, biases, and uncertainties are summarized in Table 4-3.

Table 4-2
Selected Coefficients for Human Health Effects Associated with Sulfate Concentration Changes

Health Effect Category	Selected Concentration-Response (probability weights)
Annual mortality risk per 1 $\mu g/m^3$ change in annual average SO_4 concentration. Sources: See Table 4-1	L 8×10^{-6} (25%) L-C 24×10^{-6} (25%) H-C 56×10^{-6} (25%) H 112×10^{-6} (25%)
Chronic bronchitis (CB) annual risk per 1 $\mu g/m^3$ change in annual average SO_4 concentration. Source: Abbey et al. (1995)	For population 25 years and over: L 0.5×10^{-4} (25%) C 1.1×10^{-4} (50%) H 2.0×10^{-4} (25%)
Respiratory hospital admissions (RHA) annual risk factors per 1 $\mu g/m^3$ change in annual average SO_4 concentration. Source: Burnett et al. (1995)	L 1.3×10^{-5} (25%) C 1.6×10^{-5} (50%) H 1.8×10^{-5} (25%)
Cardiac hospital admissions (CHA) annual risk per 1 $\mu g/m^3$ change in annual average SO_4 concentration. Source: Burnett et al. (1995)	L 1.0×10^{-5} (25%) C 1.3×10^{-5} (50%) H 1.7×10^{-5} (25%)
Asthma symptom day (ASD) annual risk factors given a 1 $\mu g/m^3$ change in annual average SO_4 concentration. Source: Ostro et al. (1991)	For population with asthma (4.7% of population): L 3.3×10^{-1} (33%) C 6.7×10^{-1} (34%) H 9.9×10^{-1} (33%)
Restricted activity day (RAD) annual risk factors given a 1 $\mu g/m^3$ change in annual average SO_4 concentration. Sources: Ostro (1987), Ostro and Rothschild (1989)	For population aged 18 years and over: L 4.7×10^{-2} (33%) C 9.3×10^{-2} (34%) H 14.6×10^{-2} (33%)
Day with lower respiratory symptom (LRS) annual risk factors given a 1 $\mu g/m^3$ change in annual average SO_4 concentration. Source: Ostro et al. (1993)	For population aged 18 and over: L 6.6×10^{-2} (25%) C 16.4×10^{-2} (50%) H 23.0×10^{-2} (25%)

Table 4-3
Key Omissions, Biases, and Uncertainties

Omissions/Biases/Uncertainties	Direction of Potential Error	Comments
Concentration-response relationships	?	Statistical association in epidemiology studies does not prove causation. Measurement error and averting behavior could cause downward bias. Omitted confounding variables could cause upward bias.
Transfer of concentration-response relationships	?	Estimates are based on transfers across time and location. Possible unaccounted for differences add uncertainty.
Relationship between sulfates and other measures of particulate matter	+	Collinearity among particulate matter measures add uncertainty to the quantitative interpretation of sulfate based results. This uncertainty is addressed in the sensitivity analysis.
Zero threshold assumption	+	Evidence on possible thresholds is inconclusive. This uncertainty is addressed in the sensitivity analysis.
Age group assumptions	-	The effect of sulfates on mortality for different age groups was based on the results of nonsulfate studies. Effects on children probably understated due to limited studies that include children.
Presumed linearity of concentration-response	?	The effect of assuming a constant risk per unit of sulfate is difficult to assess with available information. Error could occur in either direction.
Assumed independence of baseline health incidence and sulfate concentrations	?	Used average incidence to transform % change/sulfate to the number of cases per change in sulfate concentration. There is no bias if they are independent.
Overall Impact	+	No clear directional bias is entirely dominant, but tendency may be toward upward bias. This is addressed in the sensitivity analyses.